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<p>(21) International Application Number: PCT/EP97/03432 (22) International Filing Date: 1 July 1997 (01.07.97) (30) Priority Data: 9614718.6 12 July 1996 (12.07.96) GB (71) Applicant (for all designated States except US): BAYER AKTIENGESELLSCHAFT [DE/DE]; D-51368 Leverkusen (DE). (72) Inventors; and (75) Inventors/Applicants (for US only): BRÄUNLICH, Gabriele [DE/DE]; Claudiusweg 9, D-42115 Wuppertal (DE). ES-SAYED, Mazen [DE/DE]; Claudiusweg 3, D-42115 Wuppertal (DE). FISCHER, Rüdiger [DE/DE]; Christian-Gau-Strasse 33, D-50933 Köln (DE). HENNING, Rolf [DE/DE]; Siebengebirgstrasse 14, D-53343 Wachtberg (DE). FUG-MANN, Burkhard [DE/DE]; Dr.-Kessel-Strasse 3, D-40878 Ratingen (DE). SCHNEIDER, Stephan [DE/DE]; Paul-Ehrlich-Strasse 2, D-42113 Wuppertal (DE). SPERZEL, Michael [DE/DE]; Normannenstrasse 31, D-42275 Wuppertal (DE). STURTON, Graham [GB/GB]; 184 Windsor Road, Bray Maidenhead SL 62 DW (GB). FITZGERALD, Mary [GB/GB]; 2 Paternoster Court, Cassington Road, Yarnton, Oxford OX51 QB (GB). BRIGGS, Barbara [GB/GB]; 24</p>		<p>Latchmere Road, Kingston-upon-Thames, Surrey KT25 TW (GB). CONCEPCION, Arnel [PH/JP]; 3-6-27, City Homes Shin-Omiya 207, Shibatsuji-cho, Nara 639 (JP). (74) Common Representative: BAYER AKTIENGESELLSCHAFT; D-51368 Leverkusen (DE). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, VZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: 3-UREIDO-PYRIDOFURANS AND -PYRIDOTHIOPHENES FOR THE TREATMENT OF INFLAMMATORY PROCESSES</p>		
<p>(57) Abstract 3-Urea-pyridofurans and -pyridothiophenes are prepared by reacting appropriately substituted 3-amino-pyridofurans or -pyridothiophenes with isocyanates or isothiocyanates. The 3-urea-pyridofurans and -pyridothiophenes can be used as active ingredients in medicaments, particularly in medicaments for the treatment of acute and chronic inflammatory processes.</p>		

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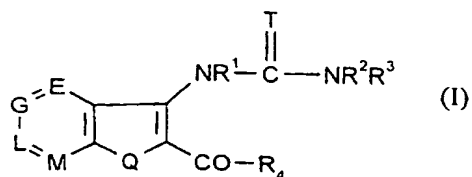
3-UREIDO-PYRIDOFURANS AND -PYRIDOTHIOPHENES FOR THE TREATMENT OF INFLAMMATORY PROCESSES

5 The invention relates to 3-urea-pyridofurans and -pyridothiophenes, processes for their preparation and their use in medicaments.

10 It is known that the NADPH oxidase of phagocytes is the physiological source to the superoxide radical anion and reactive oxygen species derived therefrom which are important in the defence against pathogens. Moreover, both inflammatory (e.g. $\text{TNF}\alpha$, IL-1 or IL-6) and anti-inflammatory cytokines (e.g. IL-10) play a pivotal role in host defence mechanisms. Uncontrolled production of inflammatory mediators can lead to acute and chronic inflammation, tissue damage, multi-organ failures and to death. It is additionally known that elevation of phagocyte cyclic AMP leads to inhibition of oxygen radical production and that this cell function is more sensitive than others such as aggregation or enzyme release.

15 Benzofuran- and benzothiophene derivatives having lipoxygenase-inhibiting action are described in the publication EP 146 243.

The invention relates to 3-urea-pyridofurans and -pyridothiophenes of the general formula (I)



20 in which

E, G, L and M are identical or different and represent a nitrogen atom or a residue of a formula -C-A, wherein at least one of the substituents E, G, L or M must represent a nitrogen atom and wherein

25 A represents hydrogen, straight-chain or branched acyl or alkoxy-carbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl, halogen, hydroxyl, straight-chain or

5 branched alkoxycarbonyl, or alkoxy each having up to 6 carbon atoms, phenoxy, benzoyl or by a group of a formula $-O-CO-CH_3$, or represents halogen, carboxyl, cyano, nitro, trifluoromethyl, trifluoromethoxy or a group of a formula $-OR^5$, $-S(O)_nR^6$, $-(O-CH_2-CO)_b-NR^7R^8$, $-CO-NR^9R^{10}$, $-SO_2-NR^{11}R^{12}$ or $-NH-SO_2R^{13}$,

in which

10 R^6 , R^8 , R^{10} and R^{12} are identical or different and
denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, benzyl or a 5 to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally substituted by identical or different substituents from the series comprising halogen, cyano, nitro or by a straight-chain or branched alkyl having
15 up to 6 carbon atoms or

denote straight-chain or branched alkenyl or acyl each having up to 8 carbon atoms, or

20 denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, halogen, carboxy or straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms,

R^7 , R^9 and R^{11} are identical or different and
denote hydrogen or a straight-chain or branched alkyl having up to 4 carbon atoms,

25 or

R^7 and R^8 together with the nitrogen atom form a 5- to 6-membered heterocycle,

R^5 has the abovementioned meaning of R^6 , R^8 , R^{10} or R^{12} and is identical or different from the latter,

or

5
10
15
20
25

R^5 denotes a hydroxyl protecting group or straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms, or denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by carboxyl, hydroxyl, straight-chain or branched acyl, oxyacyl or alkoxy-carbonyl each having up to 6 carbon atoms, phenoxy, benzoyl or by a 5- to 7-membered unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O, which is optionally substituted by halogen, cyano, nitro, or by straight-chain or branched alkyl having up to 6 carbon atoms,

and/or alkyl is substituted by a group of a formula
 $-(CO)_c-NR^{14}R^{15}$

15
20
25

in which

R^{14} and R^{15} are identical or different and have the above-mentioned meaning of R^7 and R^8

and

c denotes a number 0 or 1,

20
25

or

R^5 denotes a group of the formula $-SO_2-R^{16}$

R^{16} denotes phenyl, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms,

a denotes a number 0, 1 or 2,

b denotes a number 0 or 1,

R^{13} has the abovementioned meaning of R^{16} and is identical or different from the latter.

or

E and G represent the CH-group

5 and

L and M represent a residue of a formula -CD and -CD'

in which

D and D' together form a pyridine ring,

10 R^1 represents hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, an aminoprotecting group or a group of the formula -CO- R^{17}

in which

15 R^{17} denotes hydroxyl, straight chain or branched alkoxycarbonyl having up to 6 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by halogen, carbonyl or straight chain or branched alkoxycarbonyl having up to 6 carbon atoms, or

20 denotes phenyl, which is optionally substituted by hydroxyl, carbonyl or straight chain or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms,

T represents an oxygen or sulfur atom,

25 R^2 and R^3 are identical or different and represent hydrogen, cycloalkyl having up to 6 carbon atoms, straight chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 8 carbon atoms, or represent benzoyl or aryl having 6 to 10 carbon atoms, which are optionally monosubstituted to trisubstituted by identical or different sub-

stituents from the series comprising halogen, cyano, nitro, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxycarbonyl or acyl each having up to 6 carbon atoms, or represent a group of a formula $-P(O)(OR^{18})(OR^{19})$,

5 in which

R^{18} and R^{19} are identical or different and denote hydrogen or straight chain or branched alkyl having up to 6 carbon atoms,

or

10 R^2 and R^3 together with the nitrogen atom form a 5- to 7-membered saturated heterocycle optionally having a further O atom,

and

15 R^4 represents aryl having 6 to 10 carbon atoms or represents a 5 to 7 membered, saturated or unsaturated heterocycle, which can contain up to 4 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further a benzene ring can be fused and wherein both rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 8 carbon atoms or by straight-chain or
20 branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms or by a group of a formula $-NR^{20}R^{21}$, $-SR^{22}$, SO_2R^{23} or $-O-SO_2R^{24}$,

25 in which

R^{20} and R^{21} have the meaning shown above for R^7 and R^8 ,

or

R²⁰ denotes hydrogen,

and

R²¹ denotes straight-chain or branched acyl having up to 6 carbon atoms,

5 R²² denotes straight-chain or branched alkyl having up to 6 carbon atoms,

10 R²³ and R²⁴ are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having up to 6 carbon atoms,

Q represents an oxygen or sulfur atom,

and salts thereof.

15 The 3-urea-pyridofurans and -pyridothiophenes according to the invention can also be present in the form of their salts and pyridinium salts. In general, salts with organic or inorganic bases or acids may be mentioned here.

20 Physiologically acceptable salts are preferred in the context of the present invention. Physiologically acceptable salts of the 3-urea-pyridofurans and -pyridothiophenes can be metal or ammonium salts of the substances according to the invention, which contain a free carboxylic group. Those which are particularly preferred are, for example, sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia, or organic amines, such as, for example, ethylamine, di- or triethylamine, di- or triethanolamine, dicyclohexylamine, dimethylaminoethanol, arginine, lysine or ethylenediamine.

25 Physiologically acceptable salts can also be salts of the compounds according to the invention with inorganic or organic acids. Preferred salts here are those with inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulphuric acid, or salts with organic carboxylic or sulphonic acids such as, for example, acetic acid, maleic acid, fumaric acid, malic acid, citric

acid, tartaric acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid or naphthalenedisulphonic acid. Preferred pyridinium salts are salts in combination with halogen.

5 The compounds according to the invention can exist in stereoisomeric forms which either behave as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemate forms, as well as the diastereomer mixtures. The racemate forms, like the diastereomers, can be separated into the stereoisomerically uniform constituents in a known manner.

10 Heterocycle in general represents a 5- to 7-membered saturated or unsaturated, preferably 5- to 6- membered, saturated or unsaturated ring which can contain up to 4 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further aromatic ring can be fused.

15 The following are mentioned as preferred: thienyl, furyl, pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, quinazolyl, quinoxazolyl, cinnolyl, thiazolyl, dihydrothiazolyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, oxazolyl, benzoxazolyl, isoxazolyl, imidazolyl, benzimidazolyl, indolyl, morpholinyl, pyrrolidinyl, piperidyl, piperazinyl, oxazolyl, oxazolinyl or triazolyl.

20 Amino protective group in the context of the above mentioned definition in general represents a protective group from the series comprising:
benzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 3,5-dimethoxybenzyloxycarbonyl, 2,4-dimethoxybenzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 4-nitrobenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl, 2-nitro-4,5-dimethoxybenzyloxycarbonyl, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl,
25 butoxycarbonyl, isobutoxycarbonyl, tert.butoxycarbonyl, allyloxycarbonyl, vinylloxycarbonyl, 2-nitrobenzyloxycarbonyl, 3,4,5-trimethoxybenzyloxycarbonyl, cyclohexoxycarbonyl, 1,1-dimethylethoxycarbonyl, adamantylcarbonyl, phthaloyl, 2,2,2-trichlorethoxycarbonyl, 2,2,2-trichlor-tert.butoxycarbonyl, menthyloxycarbonyl, phenoxycarbonyl, 4-nitrophenoxycarbonyl, fluorenyl-9-methoxycarbonyl, formyl,
30 acetyl, propionyl, pivaloyl, 2-chloracetyl, 2-bromacetyl, 2,2,2-trifluoracetyl, 2,2,2-trichloracetyl, benzoyl, 4-chlorobenzoyl, 4-bromobenzoyl, 4-nitrobenzoyl, phthalimido, isovaleroyl oder benzyloxymethylen, 4-nitrobenzyl, 2,4-dinitrobenzyl or 4-nitrophenyl.

Preferred compounds of the general formula (I) are those

in which

5 E, G, L and M are identical or different and represent a nitrogen atom or a residue of a formula -C-A, wherein at least one of the substituents E, G, L or M must represent a nitrogen atom and wherein

10 A represents hydrogen, straight-chain or branched acyl or alkoxycarbonyl each having up to 6 carbon atoms, or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by chlorine, bromine, hydroxyl, carboxyl, straight-chain or branched alkoxycarbonyl or alkoxy each having up to 5 carbon atoms, phenoxy, benzoyl, or by a group of a formula -O-CO-CH₃, or represents fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR⁵, -S(O)_nR⁶, (O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³,

15 in which

20 R⁶, R⁸, R¹⁰ and R¹² are identical or different and denote hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by a straight-chain or branched alkyl having up to 5 carbon atoms,

25 denote straight-chain or branched alkyl, alkenyl or acyl each having up to 6 carbon atoms, or denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms,

30 R⁷, R⁹ and R¹¹ are identical or different and

denote hydrogen or a straight-chain or branched alkyl having up to 3 carbon atoms,

or

5 R^7 and R^8 together with the nitrogen atom form a pyrrolidiny1 or piperidiny1 ring,

R^5 has the abovementioned meaning of R^6 , R^8 , R^{10} or R^{12} and is identical or different from the latter,

or

10 R^5 denotes benzyl, acetyl or tetrahydropyrany1 or straight chain or branched alkoxy carbonyl having up to 4 carbon atoms, denotes straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl, hydroxyl, straight-chain or branched acyl, oxyacyl or alkoxy carbonyl each having up to 4 carbon atoms, phenoxy, 15 benzoyl or by pyridyl, imidazolyl, thenyl or furyl, which are optionally substituted by fluorine, chlorine, bromine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms,

20 and/or alkyl is substituted by a group of a formula $-(CO)_c-NR^{14}R^{15}$,

in which

R^{14} and R^{15} are identical or different and have the above mentioned meaning of R^7 and R^8 ,

and

25 c denotes a number 0 or 1,

or

R^5 denotes a group of a formula $-SO_2R^{16}$,

in which

R^{16} denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 3 carbon atoms,

5 a denotes a number 0, 1 or 2,

 b denotes a number 0 or 1,

R^{13} has the abovementioned meaning of R^{16} and is identical or different from the latter,

or

10 E and G represent the CH-group,

and

L and M represent a residue of a formulae $-CD$ and $-CD'$,

in which

D and D' together form a pyridine ring,

15 R^1 represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, tert.butoxycarbonyl or a group of the formula $-CO-R^{17}$

in which

20 R^{17} denotes hydroxyl, straight chain or branched alkoxycarbonyl having up to 4 carbon atoms, cyclopentyl, cyclohexyl, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by fluorine, chlorine, bromine, carboxyl or straight chain or branched alkoxycarbonyl having up to 4 carbon atoms, or

denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

T represents an oxygen or sulfur atom,

5 R² and R³ are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 6 carbon atoms, or
represent benzoyl or phenyl, which are optionally monosubstituted to
10 trisubstituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, carboxyl, cyano, nitro or by a straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms, or
represent a group of a formula -P(O)(OR¹⁸)(OR¹⁹)

in which

15 R¹⁸ and R¹⁹ are identical or different and denote straight chain or branched alkyl having up to 4 carbon atoms

or

R² and R³ together with the nitrogen atom form a pyrrolidinyl, piperidinyl or morpholinyl ring,

20 and

R⁴ represents phenyl or
represents pyridyl, pyrimidyl, pyrrol, imidazolyl, pyrazolyl, thienyl, iso-
thiazolyl, pyrazinyl, thiazolyl or benzo[b]thiophenyl, wherein both rings are
optionally monosubstituted to trisubstituted by identical or different sub-
25 stituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 6 carbon atoms, or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally

substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms,

and

Q represents an oxygen or sulfur atom,

5 and salts thereof.

Particularly preferred compounds of the general formula (I) are those,

in which

10 E, G, L and M are identical or different and represent a nitrogen atom or a residue of a formula -C-A, wherein at least one of the substituents is E, G, L or M, must represent a nitrogen atom and wherein

15 A represents hydrogen, acetyl, straight-chain or branched alkoxy, or alkoxy carbonyl having up to 4 carbon atoms, straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by bromine or by a group of a formula O-CO-CH₃, methoxy or hydroxyl
or

20 represents fluorine, chlorine, bromine, carboxyl, cyano, hydroxyl, nitro, trifluoromethyl, or a group of the formula -OSO₂-CH₃, -OCH₂-CH=CH₂, -O-CH₂-CO-pyrrolidine, -O(CH₂)₂-pyrrolidine, -O(CH₂)₂-piperidine, -O-(CH₂)₄-O-C(O)-CH₃ or -O-(CH₂)₂-O-C(O)-CH₃

or

E and G represents the CH-group,

and

25 L and M represent a residue of a formulae -CD and -CD'

in which

D and D' together form a pyridine ring,

R¹ represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

5 T represents an oxygen or sulfur atom,

R² and R³ are identical or different and represent hydrogen, straight-chain or branched alkyl having up to 5 carbon atoms, or represent benzoyl or phenyl, or represent a group of a formula -P(O)(OC₂H₅)₂,

10 and

R⁴ represents phenyl or represents pyridyl, pyrimidyl, furyl, thienyl, imidazolyl, pyrrolyl, thiazolyl or pyrazinyl which are optionally up to difold substituted by identical or different pyridyl, nitro, fluorine, chlorine, bromine, methoxy, trifluoromethyl, cyano, or by straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms

15

and

Q represents an oxygen or sulfur atom,

20 and salts thereof.

Very particularly preferred are those compounds of the general formula (I),

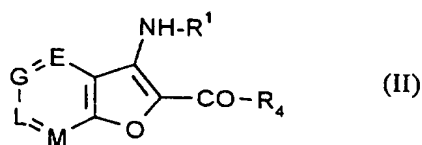
in which

R¹ and R² represent hydrogen,

R^4 represents phenyl, pyridyl or thienyl, which are optionally mono- or disubstituted by chlorine, bromine, fluorine, nitro, methoxy or straight-chain or branched alkyl having up to 3 carbon atoms.

5 A process for the preparation of the compounds of the general formula (I) has additionally been found, characterized in that

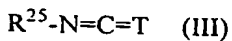
compounds of the general formula (II)



in which

E, G, L, M, R^1 and R^4 have the abovementioned meaning

10 are reacted with compounds of the general formula (III)



in which

T has the abovementioned meaning

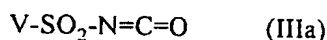
and

15 R^{25} has the abovementioned meaning of R^2 and R^3

in inert solvents, if appropriate in the presence of a base and/or in the presence of an auxiliary,

and in the case of $R^2/R^3 = H$ and $T = O$,

20 compounds of the general formula (II) are reacted with compounds of the general formula (IIIa)



in which

V denotes halogen, preferably chlorine,

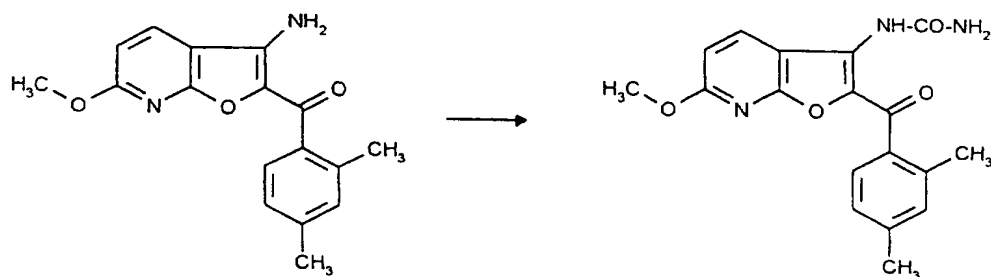
and in the case of $R^2/R^3 = H$ and $T = S$,

5 compounds of the general formula (II) are reacted with NH_4SCN ,

and in case of R^1, R^2 and/or $R^3 \neq H$ the amino groups are derivated optionally by customary methods.

and in the case of $A = O-SO_2R^{16}$ the corresponding hydroxyl compounds are reacted with sulfonyl chloride derivatives in presence of K_2CO_3 .

10 The process according to the invention can be illustrated by way of example by the following equations:



Suitable solvents are generally customary organic solvents which do not change under the reaction conditions. These include ethers such as diethyl ether, dioxane or tetrahydrofurane, ethylacetate, acetone, dimethylsulfoxide, dimethylformamide
15 or alcohols such as methanol, ethanol, propanol or halogenohydrocarbons such as dichloromethane, dichloroethane, trichloromethane or tetrachloromethane. Dichloromethane is preferred.

Suitable bases are generally inorganic or organic bases. These preferably include
20 alkali metal hydroxides such as, for example, sodium hydroxide, sodium hydrogen-carbonate or potassium hydroxide, alkaline earth metal hydroxides such as, for

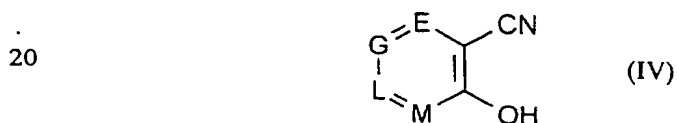
example, barium hydroxide, alkali metal carbonates such as sodium carbonate, potassium carbonate, alkaline earth metal carbonates such as calcium carbonate, or alkaline metal or organic amines (trialkyl(C₁-C₆)amines) such as triethylamine, or heterocycles such as 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or amides such as sodium amides, lithium butyl amide or butyllithium, pyridine or methyldiethylamine. It is also possible to employ alkali metals, such as sodium or its hydrides such as sodium hydride, as bases. Potassium carbonate, triethylamine, sodium hydrogencarbonate and sodium-hydroxide are preferred.

10 The process is in general carried out in a temperature range from -30°C to +100°C, preferably from -10°C to +50°C.

The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

15 The base is employed in an amount from 1 mol to 10 mol, preferably from 1.0 mol to 4 mol, relative to 1 mol of the compounds of the general formulae (III) or (IIIa).

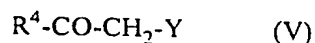
The compounds of the general formula (II) are in the case of E = N new or are prepared by at first reacting compounds of the general formula (IV)



in which

E, G, L and M have the above mentioned meaning

with compounds of the general formula (V)



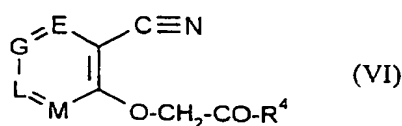
25 in which

R^4 has the abovementioned meaning

and

Y represents a typical leaving group such as, for example, chlorine, bromine, iodine, tosylate or mesylate, preferably bromine,

5 to form compounds of the general formula (VI)



in which

E, G, L, M and R^4 have the abovementioned meaning,

and followed by cyclisation,

10 in one of the abovementioned solvents and bases, preferably potassium carbonate and dimethylformamide or acetone, and in the case of $R^1 \neq H$ the abovementioned substituents are introduced by customary methods.

The process is in general carried out in a temperature range from $+10^\circ\text{C}$ to $+150^\circ\text{C}$, preferably from $+50^\circ\text{C}$ to $+100^\circ\text{C}$.

15 The process is generally carried out at normal pressure. However, it is also possible to carry out it at elevated pressure or at reduced pressure (for example in a range from 0.5 to 5 bar).

20 Suitable bases are the customary inorganic bases. These preferably include alkali metal hydroxides or alkaline earth metal hydroxides such as, for example, sodium hydroxide, potassium hydroxide or barium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate or sodium hydrogen carbonate, or alkali metal alkoxides such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide or potassium tert.butoxide. Sodium hydroxide or potassium hydroxide are particularly preferably employed.

5 Suitable solvents are water or the organic solvents customary for hydrolysis. These preferably include alcohols such as methanol, ethanol, propanol, isopropanol or butanol, or ethers such as tetrahydrofuran or dioxane, or dimethylformamide, or dimethyl sulphoxide. Alcohols such as methanol, ethanol, propanol or isopropanol are particularly preferably used. It is also possible to employ mixtures of the solvents mentioned.

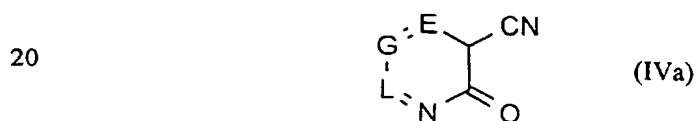
The reaction can also be carried out with acids such as, for example, trifluoroacetic acid, acetic acid, hydrochloric acid, hydrobromic acid, methanesulphonic acid, sulphuric acid or perchloric acid, preferably with trifluoroacetic acid.

10 The reaction is in general carried out in a temperature range from 0°C to +180°C, preferably from +20°C to +160°C.

In general, the reaction is carried out at normal pressure. However, it is also possible to work at reduced pressure or at elevated pressure (for example from 0.5 to 5 bar).

15 When carrying out the reaction, the base is in general employed in an amount from 1 to 3 mol, preferably from 1 to 1.5 mol, relative to 1 mol of the ester. Molar amounts of the reactants are particularly preferably used.

Compounds of the general formula (II) in which M denotes a nitrogen atom are prepared by reacting compounds of the general formula (IVa)

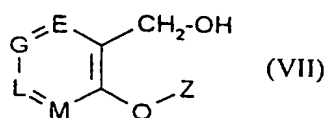


in which

E, G and L have the abovementioned meaning,

in analogy to the abovementioned process.

25 The compounds of the general formula (IV) are new or can be prepared by at first reacting compounds of the general formula (VII)



in which

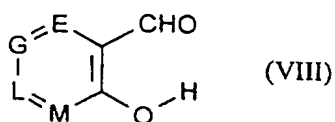
E, G, L and M have the abovementioned meaning

and

5 Z prerepresents C₁-C₄-alkyl

with MnO₂ and followed by BCl₃ /dimethylaminopyridine,

to form compounds of the general formula (VIII)



in which

10 E, G, L and M have the abovementioned meaning

and in a last step are reacting with NH₂OH / HCl / HCOOH.

The reaction is in general carried out in a temperature range from 0°C to +180°C, preferably from +20°C to +160°C.

15 In general, the reaction is carried out at normal pressure. However, it is also possible to work at reduced pressure or at elevated pressure (for example from 0.5 to 5 bar).

The compounds of the general formula (VII) are new or are prepared by customary methods for example by reducing of the corresponding carboxylgroup by LiAlH₄ in one of the abovementioned ethers.

The compounds of the general formulae (III), (IIIa), (IV), (IVa) and (V) are known or can be prepared by customary methods.

The compounds of the general formulae (VI) and (VIII) are new or can be prepared like described above.

5 Surprisingly it was found that compounds given by the general formula (I) inhibited oxygen radical formation as well as $\text{TNF}\alpha$ (tumor necrosis factor) production. These compounds elevated cellular cyclic AMP probably by inhibition of phagocyte phosphodiesterase activity.

10 The compounds according to the invention specifically inhibit the production of superoxide by polymorphonuclear leukocytes (PMN). Furthermore, these compounds inhibit $\text{TNF}\alpha$ release in human monocytes in response to a variety of stimuli including bacterial lipopolysaccharide (LPS), complement-opsonized zymosan (ZymC3b) and $\text{IL-1}\beta$. The described effects are probably mediated by the elevation of cellular cAMP probably due to inhibition of the type IV phospho-
15 diesterase responsible for its degradation.

They can therefore be employed in medicaments for the treatment of acute and chronic inflammatory processes.

20 The compounds according to the invention are preferably suitable for the treatment and prevention of acute and chronic inflammation and auto immune diseases, such as emphysema, alveolitis, shock lung, all kind of COPD, ARDS, asthma and bronchitis, cystic fibrosis, eosinophilic granuloma, arteriosclerosis, arthrosis, inflammation of the gastro-intestinal tract, myocarditis, bone resorption diseases, reperfusion injury, Crohn's disease, ulcerative colitis, system lupus erythematosus, type I diabetes mellitus, psoriasis, anaphylactoid purpura nephritis, chronic
25 glomerulonephritis, inflammatory bowel disease, other benign and malignant proliferative skin diseases, atopic dermatitis, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, arterial restenosis, sepsis and septic shock, toxic shock syndrome, grafts vs host reaction, allograft rejection, treatment of cytokine mediated chronic tissue degeneration, rheumatoid arthritis, arthritis, rheumatoid
30 spondylitis and osteoarthritis and coronary insufficiency, myalgias, multiple sclerosis, malaria, AIDS, cachexia, prevention of tumor growth and invasion of tissue, leukemia, depression, memory impairment and acute stroke. The

compounds according to the invention are additionally suitable for reducing the damage to infarct tissue after reoxygenation. In this case the simultaneous administration of allopurinol to inhibit xanthine oxidase is of advantage. Combination therapy with superoxide dismutase is also of use.

5 Test description

1. Preparation of human PMN

Blood was taken from healthy subjects by venous puncture and neutrophils were purified by dextran sedimentation and resuspended in the buffered medium.

- 10 2. Inhibition of FMLP-stimulated production of superoxide radical anions.
Neutrophils ($2.5 \times 10^5 \text{ ml}^{-1}$) were mixed with cytochrome C (1.2 mg/ml) in the wells of a microtitre plate. Compounds according to the invention were added in dimethyl sulphoxide (DMSO). Compound concentration ranged from 2.5 nM to 10 μM , the DMSO concentration was 0.1% v/v in all wells. After addition of cytochalasin b ($5 \mu\text{g} \times \text{ml}^{-1}$) the plate was incubated for 5 min at 37°C. Neutrophils were then stimulated by addition of $4 \times 10^{-8} \text{ M}$ FMLP and superoxide generation measured as superoxide dismutase inhibitable reduction of cytochrome C by monitoring the OD_{550} in a Thermomax microtitre plate spectrophotometer. Initial rates were calculated using a Softmax kinetic calculation programme. Blank wells contained 200 units of superoxide dismutase.

The inhibition of superoxide production was calculated as follows:

$$\frac{[1 - ((\text{Rx} - \text{Rb}))]}{((\text{Ro} - \text{Rb}))} \times 100$$

Rx = Rate of the well containing the compound according to the invention.

Ro = Rate in the control well.

Rb = Rate in the superoxide dismutase containing blank well.

Compounds according to the invention have IC_{50} values in the range $0,07 \mu M$ - $10 \mu M$.

3. Measurement of PMN cyclic AMP concentration

5 The compounds according to the invention were incubated with 3.7×10^6 PMN for 5 min at $37^\circ C$ before addition of 4×10^{-8} M FMLP. After 6 min protein was precipitated by the addition of 1% v/v conc. HCl in 96% v/v ethanol containing 0.1 mM EDTA. After centrifugation the ethanolic
10 extracts were evaporated to dryness under N_2 and resuspended in 50 mM Tris/HCl pH 7.4 containing 4 mM EDTA. The cyclic AMP concentration in the extracts was determined using a cyclic AMP binding protein assay supplied by Amersham International plc. Cyclic AMP concentrations were expressed as percentage of vehicle containing control incubations.

Compounds elavate the cAMP-level at $1 \mu M$ compound 0-400% of control values.

15 4. Assay of PMN phosphodiesterase

This was performed as a particulate fraction from human PMN essentially as described by Souness and Scott (Biochem. J. 291, 389-395, 1993). Particulate fractions were treated with sodium vanadate / glutathione as
20 described by the authors to express the descrete stereospecific site on the phosphodiesterase enzyme. Compounds according to the invention had IC_{50} values ranging from $0,001 \mu M$ to $10 \mu M$.

5. Assay of human platelet phosphodiesterase

25 This was performed essentially as described by Schmidt et al (Biochem. Pharmacol. 42, 153-162, 1991) except that the homogenate was treated with vanadate glutathione as above. Compounds according to the invention had IC_{50} values greater than $100 \mu M$.

6. Assay of binding to the rolipram binding site in rat brain membranes

30 This was performed essentially as described by Schneider et al. (Eur. J. Pharmacol. 127, 105-115, 1986). Compounds according to the invention had IC_{50} values in the range $0,01$ to $10 \mu M$.

7. Preparation of human monocytes

Blood was taken from normal donors. Monocytes were isolated from peripheral blood by density centrifugation, followed by centrifugal elutriation.

8. Endotoxin induced TNF release
- 5 Monocytes ($1 \times 10^6 \text{ ml}^{-1}$) were stimulated with LPS ($2 \mu\text{g ml}^{-1}$) and coincubated with the compounds at different concentrations (10^{-4} to $10 \mu\text{g ml}^{-1}$). Compounds were dissolved in DMSO/medium (2% v/v). The cells were incubated in RPMI-1640 medium glutamine/FCS supplemented and at 37°C in a humidified atmosphere with 5% CO_2 . After 18 to 24
- 10 hours TNF was determined in the supernatants by an human TNF specific ELISA (medgenix). Controls were nonstimulated and LPS stimulated monocytes without compounds. Example 2, 13 and 16 induce inhibition of LPS driven TNF activity in human monocytes (IC_{50} : 10^{-3} to $1 \mu\text{g ml}^{-1}$).
9. Endotoxin induced shock lethality in mice
- 15 B6D2F1 mice ($n=10$) were sensitized with galactosamine (600 mg/kg), and shock and lethality were triggered by LPS ($0.01 \mu\text{g/mouse}$). The compounds were administered intravenously 1 hour prior LPS. Controls were LPS challenged mice without compound. Mice were dying 8 to 24 hours post LPS challenge. Example 1 and 9 reduced the endotoxin mediated mortality about 70% to 100% at doses of 3 to 30 mg/kg.
- 20

The galactosamine / LPS mediated mortality was reduced.

10. Eosinophilia infiltration model
- Compounds of the invention were administered orally to sensitised guinea-pigs at -20, -1 and +6 hours prior to antigen challenge. At 24 hours post
- 25 antigen challenge the lungs were lavaged and inflammatory cells isolated by centrifugation. The resultant pellet was lysed and the lysate assayed for eosinophil peroxidase activity which was used as a marker for eosinophil number. Lysate eosinophil peroxidase in treated animals was compared to vehicle treated controls.
- 30 11. Bronchoconstriction model
- Bronchoconstriction was induced in mechanically ventilated guinea-pigs by administering 30 breaths of an aerosol of 0.001% w/v leukotriene D₄.

Bronchoconstriction was allowed to develop to a maximum. Compounds of the invention were administered intravenously and the reduction in bronchoconstriction measured and compared to vehicle treated controls.

5 The new active compounds can be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, nontoxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration of about 0.5 to 90%
10 by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds with solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent, organic solvents can be used as auxiliary solvents if appropriate.

15 Administration is carried out in a customary manner, preferably orally or parenterally, in particular perlingually or intravenously.

In the case of parenteral administration, solutions of the active compound can be employed using suitable liquid vehicles.

20 In general, it has proved advantageous on intravenous administration to administer amounts from about 0.001 to 10 mg/kg, preferably about 0.01 to 5 mg/kg of body weight to achieve effective results, and on oral administration the dosage is about 0.01 to 25 mg/kg, preferably 0.1 to 10 mg/kg of body weight.

25 In spite of this, it may be necessary to depart from the amounts mentioned, in particular depending on the body weight or the type of application route, on individual behaviour towards the medicament, the manner of its formulation and the time or interval at which administration takes place. Thus, in some cases it may be sufficient to manage with less than the abovementioned minimum amount, while in other cases the upper limit mentioned must be exceeded. In the case of administration of relatively large amounts, it is advisable to divide these into
30 several individual doses over the course of the day.

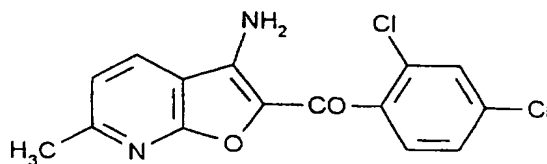
Solvents

	I	petrolether : ethylacetate	1:1
	II	petrolether : ethylacetate	5:1
	III	petrolether : ethylacetate	5:2
5	IV	ethylacetate	
	V	dichlormethane : methanol	5:1
	VI	dichlormethane	
	VII	cyclohexan : ethylacetate	3:1
	VIII	dichlormethan : methanol	50:1
10	IX	dichlormethan : methanol	20:1
	X	cyclohexan:ethylacetate	2:1

Starting compounds**Example I**

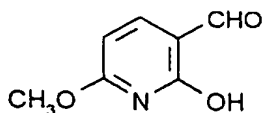
3-Amino-2-(2,4-dichlorobenzoyl)-6-methyl-7-pyridofuran

15



1.34 g (10 mmol) of 3-Cyano-6-methylpyridon, 4.14 g (30 mmol) K_2CO_3 and 3.21 g (12 mmol) of ω -Brom-2,4-dichloroacetophenone were suspended in 50 ml acetone. After reflux for 48 hours it was filtered off. The solvent was removed and the residue recrystallized from ethylacetate and dried.

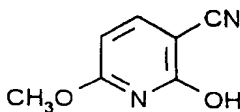
20 Yield: 0,7 g (21.8%)
mp.: 237°C

Example II**2-Hydroxy-6-methoxy-nicotinaldehyde**

5 8.4 g (0.05 mol) 2,6-dimethoxy-nicotinaldehyde was solved in 75 ml methylene chloride. At 0°C (0.2 mol) BCl₃ as 1 molar solution in methylene chloride 200 ml was added and stirred at room temperatur for 20 h. The mixture was poured on ice/water, neutralized and extracted with CH₂Cl₂. Evaporation of the solvent affords 5.7 g (75%) of the title compound.

Example III

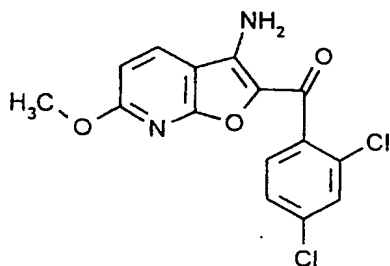
10 **2-Hydroxy-6-methoxy-nicotinonitrile**



15 5.7 g (37 mmol) of Example III, 3.1 g (44 mmol) hydroxylamine hydrochloride and 5.1 g (74 mmol) in 50 ml formic acid were stirred under reflux for 15 h. After cooling the mixture was poured on 30 ml ice/water. Extraction with ethyl acetate, evaporation of the solvent and recrystallisation with ethanol yielded 1.2 (22 %) of the title compound.
mp.: 232°C.

Example IV

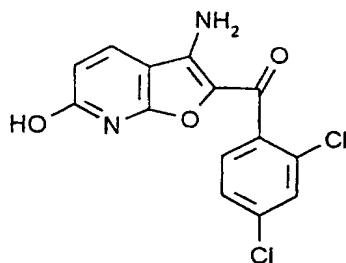
(3-Amino-6-methoxy-3a, 7a-dihydro-furo(2,3-b)-pyridin-2-yl)-(2,4-dichlorophenyl)-methanol



- 5 Starting from Example XIII, the title compound was prepared in analogy to example I.
Yield: 94 %,
mp.: 259-60°C.

Example V

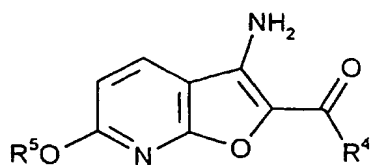
- 10 (3-Amino-6-hydroxy-3a,7a-dihydro-furo(2,3-b)pyridine-2-yl)-(2,4-dichlorophenyl)methanone



- 15 1 g (3 mmol) of Example IV was solved in 25 ml toluene. 2.8 g (21 mmol) AlCl_3 was added in portions at 25°C. The mixture was then stirred under reflux for 1 h. After cooling the mixture was poured on ice. Extraction with ethylacetate; evaporating the solvent and recrystallisation with ethylacetate yielded 0.73 g (75.3 %) of the title compound.
mp. >305°C.

The compounds shown in table I, II, III and IV are prepared in analogy to example I.

Table I:



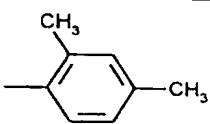
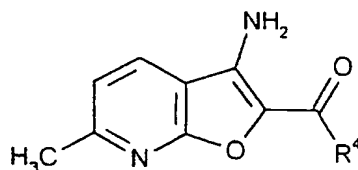
Exp.- No.	R^4	R^5	Yield (%)	mp. ($^{\circ}\text{C}$)
VI		$-\text{CH}_3$	40	184

Table II:

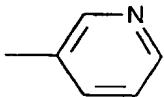
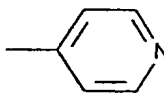
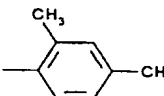
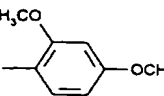
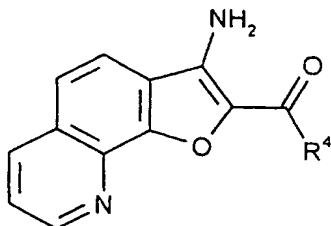
Ex.-No.	R ⁴	Yield (%)	mp. (°C)	R _f
VII		24	-	0,6 (V)
VIII		34	269	0,26 (V)
IX		50	216-7	-
X		56	188	0,19 (Cy/EE 1/1)

Table III:

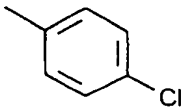
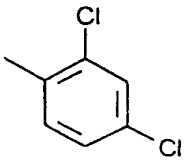
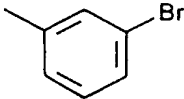
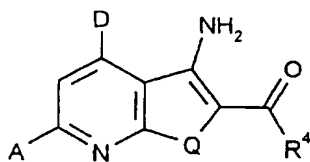
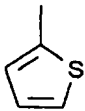
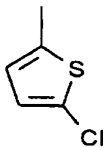
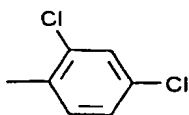
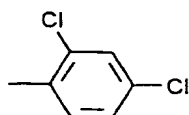
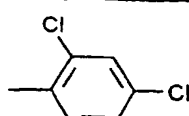
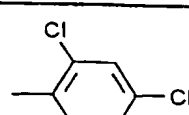
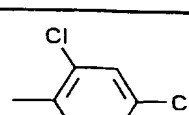
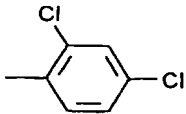
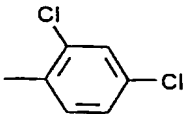
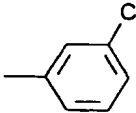
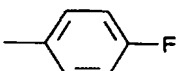

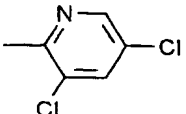
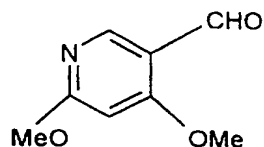
Ex.-No.	R ⁴	Yield (%)	mp. (°C)	R _f
XI		45	>300	0,51 (I)
XII		21	>300	0,8 (V)
XIII		35	233 (Z)	0,35 (I)

Table IV

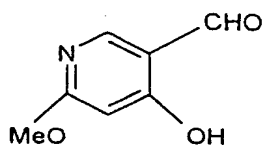
Ex.- No.	Q	R ⁴	A	D	Yield (%)	mp. (°C) /R _f
XIV	S		COCH ₃	H	22	230-32 0.62 (cyclo- hexan/THF 3:7)
XV	S		CH ₃	H	66	170-71 0.48 (cyclo- hexan/THF 3:7)
XVI	O		CH ₃	H	30	105 0.35 (VII) 0.86 (I)
XVII	O		CH ₃	H	15	195 0.93 (V) 0.17 (VII); 0.64
XVIII	O		CH ₃	CH ₃	18	128 0.93 (V); 0.14 (I)

Ex.- No.	Q	R ⁴	A	D	Yield (%)	mp. (°C) /R _F
XIX	O		CH ₃	H	9	amorph 0.12 (VII); 0.52 (I)
XX	O		CH ₃	H	20	239 0.15 (VII); 0.57 (I) 0.93 (V)
XXI	O		C ₂ H ₅	H	19	0.19 (X)
XXII	O		CH(CH ₃) ₂	H	52.6	0.2 (X)
XXIII	O		CH ₂ CH(CH ₃) ₂	H	39.2	0.19 (X)
XXIV	O		CH ₂ Br	H	38.8	0.33 (X)
XXV	O		CH ₂ OCOCH ₃	H	92	0.25 (X)

Ex. - No.	Q	R ⁴	Λ	D	Yield (%)	mp. (°C) /R _f
XXVI	O		CH ₂ OCH ₃	H	100	0.13 (X)
XXVII	O		C ₃ H ₇	H		
XXVIII	O		CH ₃	H	31	202-3
XXIX	O		CH ₃	H	51	225
XXX	O		CH ₃	H	56	255-8
XXXI	O		CH ₃	H	77	249-52

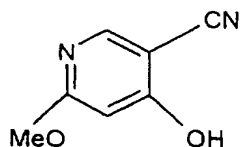
Example XXXII 4,6 Dimethoxy nicotinoaldehyde

0,63 g (3,72 mmol) of 2,4-dimethyl-5-hydroxy methyl-pyridin was dissolved in 15 ml methylene chloride. After addition of 1,3 g (14.9 mmol) of MnO_2 the mixture was refluxed for 3 hours. After cooling the mixture was filtered off. Evaporation of the solvent affords 0,48 g (96,7%) of the title compound mp: 97-8°C.

Example XXXIII 6-Hydroxy-4-methoxy-nicotinaldehyde

starting from example XXXII, the title compound was prepared in analogy to example II

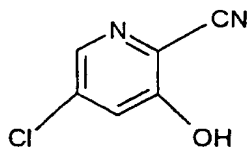
Yield: 43%, R_f 0,83 (IX)

Example XXXIV 6-Hydroxy-4-methoxy-nicotinonitrile

Starting from example XXXIII, the title compound was prepared in analogy to example III

Yield: 26%, R_f = 0,16 (IX)

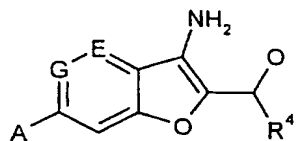
2,4-Dimethyl-6-hydroxy-nicotinonitrile,
2,4-Dimethoxy-5-hydroxymethyl-pyridin
were prepared according to the literature.

Example XXXV 4-Chloro-6-hydroxy-picolinonitrile

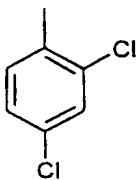
To 3-chloro-5-hydroxy-N-oxide (prepared from the corresponding pyridine using 30% H_2O_2 and acetic acid) (3.64 g, 25 mmol) in dry acetonitrile (20 ml) were added triethylamine (8.3 ml, 62.5 mmol) and trimethylsilyl cyanide (11 ml, 87.5 mmol), dropwise at rt. The resulting mixture was heated at 100 - 110°C for 8 hours. After cooling to rt, the solvent and unreacted reagents were evaporated, the residue was refluxed for 0.5 hour with hexamethyldisilazane. It was concentrated again under reduced pressure and the crude product was purified by column chromatography to afford 1.25 g (32% yield) of the desired product.

Compounds shown in Table V are prepared in analogy to example I

Table V

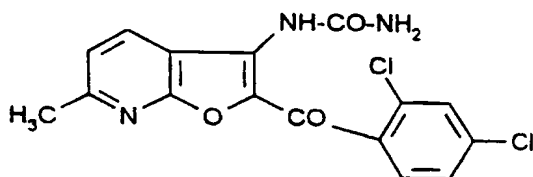


Ex.-No.	R ⁴	A	G	E	Yield	m.p.
XXXVI		-OCH ₃	N	CH	67%	173(d)
XXXVII		-CH ₃	N	C-CH ₃	94%	-
XXXVIII		-Cl	Cl	N	55%	-

Ex.-No.	R ⁴	A	G	E	Yield	m.p.
XXXIX		-CH ₃	N	C-CH ₃	40%	

Preparation Examples**Example 1**

[2-(2,4-Dichlorobenzoyl)-6-methyl-7-pyridofuran-3-yl]urea

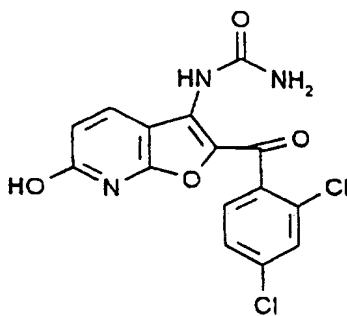


5 0.321 g (1 mmol) of Example 1 was solved in ethylacetate and 0.163 g / 0,1 ml (1.15 mmol) chlorosulfonylisocyanat was added. After 2 hours stirring at room temperature 5 ml HCl as added and stirred until the product is formed as a pre-

10 cipitate. 10 ml water was added and the precipitate filtered off. The compound was washed with water and ethanol and dried.
Yield: 0.25 g (68.9%)
mp.: 217°C

Example 2

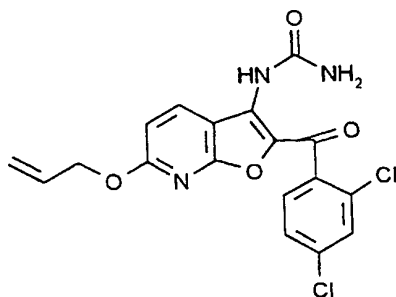
[2-(2,4-Dichloro-benzoyl)-6-hydroxy-3a,7a-dihydrofuro[2,3b]pyridin-3-yl]-urea



15 The title compound was prepared in analogy to Example 1, starting from Example 1.
Yield: 86%,
mp.: 200°C.

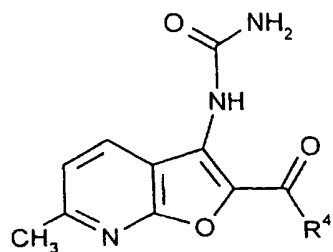
Example 3

[6-Allyloxy-2-(2,4-dichloro-benzoyl)-3a,7a-dihydrofuro[2,3-b]pyridin-3-yl]-urea



- 5 1.1 g (3 mmol) of Example 2, 0.42 g (3.45 mmol) 3-Brompropen and 0.41 g (3 mmol) K_2CO_3 were mixed in 30 ml acetone and refluxed for 3 h. After cooling the mixture was poured in 20 ml water. Extraction with ethyl acetate, evaporation of the solvent and recrystallisation with ethanol affords 0.12 g (9.8 %) of the title compound.
mp.: 222°C.

- 10 Compounds shown in table 1, 2, 3, 4, 5 and 6 are prepared in analogy to example 1, except * marked compounds in Table 3 and 6 which are prepared in analogy to Example 3.

Table 1:

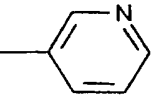
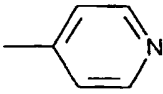
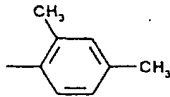
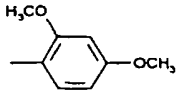
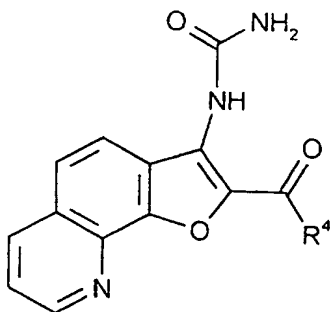
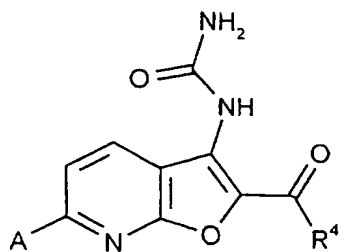
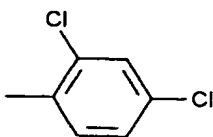
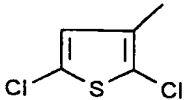
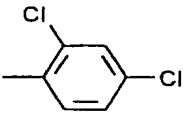

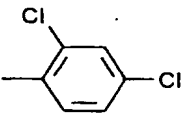

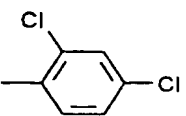
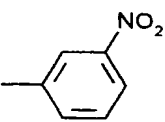
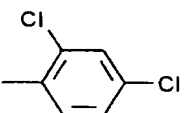
Ex.-No.	R ⁴	Yield (%)	mp. (°C)	R _f
4		56	224	-
5		10	>300	0.09 (100/5)
6		84	218	-
7		5	-	0.19 (VIII)

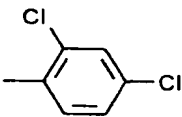
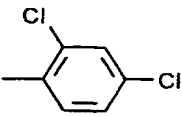
Table 2:

Ex.-No.	R ⁴	Yield (%)	mp. (°C)	R _f
8		98	214	0.08 (I)
9		92	>300	0.05 (cyclohexan/ THF 3:7)
10		90	237	0.06 (I)

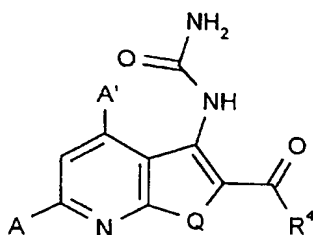
Table 3:

Ex.- No.	R ⁴	A	Yield (%)	mp. (°C)/R _f
11		-OCH ₃	82	234-6
12		-OCH ₃	59	232-4
13		-CH ₃	10	224
14*		-O-CH ₂ -CO-N	94	255

Ex. - No.	R ⁴	A	Yield (%)	mp. (°C)/R _f
15		-C ₃ H ₇	72.7	0.1 (X)
16		CH ₃	57	amorph 0.10 (VII); 0.45 (I)
17*		OCH ₂ CH ₂ N 	5	233
18*		OCH ₂ CH ₂ N 	15	210°C
19		CH ₂ OCH ₃	43	0.24 (I)
20		OCH ₃	63	246°C
21		C ₂ H ₅	12	0.116 (X)

Ex. - No.	R ⁴	A	Yield (%)	mp. (°C)/R _f
22		CH ₂ CH(CH ₃) ₂	67	0.52 (X)
23		CH(CH ₃) ₂	58	0.09 (X)

* prepared like example 33

Table 4:

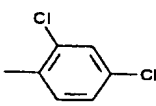
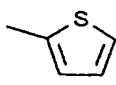
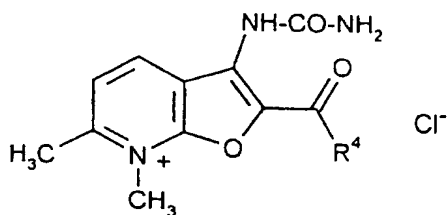
Ex.- No.	A'	R ⁴	A	Q	Yield (%)	mp. (°C)
24	H		COCH ₃	S	18	220-22
25	CH ₃		CH ₃	O		

Table 5:

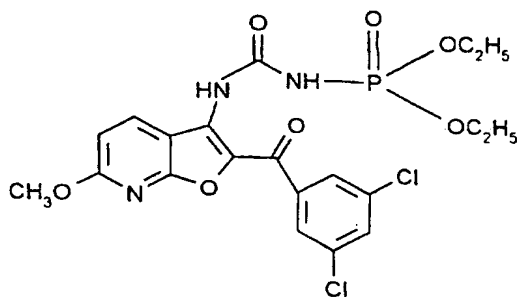
Ex.-No.	R ⁴	Yield (%)	mp. (°C)
26*		40	214

- 5 * The compound was synthesized starting from Example 1 by reaction with methyl iodide in acetone under reflux

Example 27

[2-(2,4-Dichlorobenzoyl)-6-methoxy-7-pyridofuran-3-yl]urea phosphoric acid diethylether

10



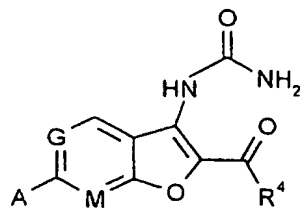
0.5 g (0.148 mmol) of Example IV was suspended in a mixture of 10 ml methylenechloride, 5 ml THF and 4 ml DMF. At 0°C 1.3 ml (8.88 mmol). Diethoxyphosphinylisocyanat was added. The reaction was refluxed for 48 hours.

40 ml methylenechloride was added and the organic layer was washed twice with 5% NaHCO_3 -solution, dried and isolated. The precipitate was washed with diethyl-ether and further purified by chromatography (methylenechloride/ethanol 40/1).

Yield: 0.625 g (81.8%)

5 $R_f = 0.40$ (methylenchloride/ethanol 40.1)

Table 6



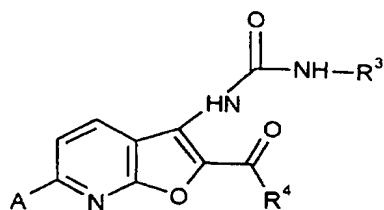
5

10

Ex.- No	A	G	M	R ⁴	Yield (% of theory)	mp.(°C)	R _f
28	-C ₂ H ₅	CH	N		63	-	0.21 (X)
29	-CH ₃	N	N		12	-	-
30	-CH ₃	N	N		34	270-2	-
31	-CH ₃	CH	N		15	258	0.13 (VIII)
32	-CH ₃	CH	N		41	>280	0.31 (IX)
33*	-OSO ₂ CH ₃	CH	N		40	219-22	-
34	-CH ₃	CH	N		60	238	0.43 (IX)
35	-CH ₃	CH	N		45	238	-
36	-CH ₃	CH	N		33	215	-

- * The compound was synthesized starting from example 2 by reaction with methansulfonyl chloride and K_2CO_3 in DMF at 80°C for 8 hours under reflux

Table 7



5

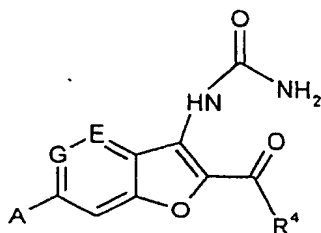
Ex.- No.	R ⁴	A	R ³	Procedure	Yield	m.p.
37			H	A	73%	
38		-CH ₃	-CH ₃	B	42%	235°C
39			H	A	60%	
40		-OCH ₃	H	B	74%	234°C
41			H	A	15%	

Procedure A: like example 33 with the corresponding alkylhalogenides and example 2 as starting material

Procedure B: like example 1

Table 8

5

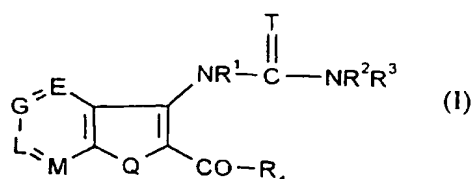


10

Ex.- No.	R ⁴	A	G	E	Yield	Procedure in analogy
42		-OCH ₃	N	CH	18%	Ex. 1
43		-CH ₃	N	C-CH ₃		Ex. 1
44		-Cl	N	N		Ex. 1

Patent Claims

1. 3-Ureido-pyridofurans and -pyridothiophenes of the general formula (I)



in which

- 5 E, G, L and M are identical or different and represent a nitrogen atom or a residue of a formula -C-A, wherein at least one of the substituents E, G, L or M must represent a nitrogen atom and wherein
- 10 A represents hydrogen, straight-chain or branched acyl or alkoxy-carbonyl each having up to 6 carbon atoms or straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl, halogen, hydroxyl, straight-chain or branched alkoxy-carbonyl, or alkoxy, each having up to 6 carbon atoms, phenoxy, benzoyl or by a group of a formula -O-CO-CH₃, or represents halogen, carboxyl, cyano, nitro, trifluoromethyl, trifluoromethoxy or a group of a formula -OR⁵, -S(O)_nR⁶, -O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³,
- 15

in which

- 20 R⁶, R⁸, R¹⁰ and R¹² are identical or different and denote hydrogen, cycloalkyl having 3 to 6 carbon atoms, benzyl or a 5 to 7-membered saturated or unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and O and to which a phenyl ring can be fused and which is optionally substituted by identical or different substituents from the series comprising halogen, cyano, nitro or by a straight-chain or branched alkyl having up to 6 carbon atoms or
- 25

denote straight-chain or branched alkenyl or acyl each having up to 8 carbon atoms, or

5 denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, halogen, carboxy or straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms,

R^7 , R^9 and R^{11} are identical or different and denote hydrogen or a straight-chain or branched alkyl having up to 4 carbon atoms,

10 or

R^7 and R^8 together with the nitrogen atom form a 5- to 6-membered heterocycle,

R^5 has the abovementioned meaning of R^6 , R^8 , R^{10} or R^{12} and is identical or different from the latter,

15 or

20 R^5 denotes a hydroxyl protecting group or straight-chain or branched alkoxycarbonyl having up to 6 carbon atoms, or denotes straight-chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by carboxyl, hydroxyl, straight-chain or branched acyl or alkoxycarbonyl each having up to 6 carbon atoms, phenoxy, benzoyl or by a 5- to 7-membered unsaturated heterocycle having up to 3 heteroatoms from the series comprising N, S and/or O, which is optionally substituted by halogen, cyano, nitro, or
25 by straight-chain or branched alkyl having up to 6 carbon atoms,

and/or alkyl is substituted by a group of a formula
 $-(CO)_c-NR^{14}R^{15}$

in which

R^{14} and R^{15} are identical or different and have the above-mentioned meaning of R^7 and R^8

and

5

c denotes a number 0 or 1,

or

R^5 denotes a group of the formula $-SO_2-R^{16}$

R^{16} phenyl, trifluoromethyl or straight-chain or branched alkyl having up to 4 carbon atoms,

10

a denotes a number 0, 1 or 2,

b denotes a number 0 or 1,

R^{13} has the abovementioned meaning of R^{16} and is identical or different from the latter.

or

15

E and G represent the CH-group

and

L and M represent a residue of a formula $-CD$ and $-CD'$

in which

D and D' together form a pyridine ring,

20

R^1 represents hydrogen, straight-chain or branched alkyl having up to 6 carbon atoms, an aminoprotecting group or a group of the formula $-CO-R^{17}$

in which

5 R^{17} denotes hydroxyl, straight chain or branched alkoxy carbonyl having up to 6 carbon atoms, cycloalkyl having 3 to 6 carbon atoms, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 8 carbon atoms, which is optionally substituted by halogen, carb-
oxy or straight chain or branched alkoxy carbonyl having up to 6 carbon atoms, or
10 denotes phenyl, which is optionally substituted by hydroxyl, carb-
oxy or straight chain or branched alkoxy or alkoxy carbonyl each having up to 6 carbon atoms,

T represents an oxygen or sulfur atom,

15 R^2 and R^3 are identical or different and represent hydrogen, cycloalkyl having up to 6 carbon atoms, straight chain or branched alkyl, alkoxy carbonyl or alkenyl each having up to 8 carbon atoms, or
represent benzoyl or aryl having 6 to 10 carbon atoms, which are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, cyano, nitro, carboxyl, straight-chain or branched alkyl, alkoxy, alkoxy carbonyl or acyl each having up to 6 carbon atoms, or
20 represent a group of a formula $-P(O)(OR^{18})(OR^{19})$,

in which

R^{18} and R^{19} are identical or different and denote hydrogen or straight chain or branched alkyl having up to 6 carbon atoms,

or

25 R^2 and R^3 together with the nitrogen atom form a 5- to 7-membered saturated heterocycle optionally having a further O atom,

and

R^4 represents aryl having 6 to 10 carbon atoms or

represents a 5 to 7 membered, saturated or unsaturated heterocycle, which can contain up to 4 oxygen, sulphur and/or nitrogen atoms as heteroatoms and to which further a benzene ring can be fused and wherein both rings are optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising hydroxyl, halogen, nitro, 1H-tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 8 carbon atoms or by straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms or by a group of a formula $-NR^{20}R^{21}$, $-SR^{22}$, SO_2R^{23} or $-O-SO_2R^{24}$,

in which

R^{20} and R^{21} have the meaning shown above for R^7 and R^8 ,

or

R^{20} denotes hydrogen,

and

R^{21} denotes straight-chain or branched acyl having up to 6 carbon atoms,

R^{22} denotes straight-chain or branched alkyl having up to 6 carbon atoms,

R^{23} and R^{24} are identical or different and represent straight-chain or branched alkyl having up to 6 carbon atoms, benzyl or phenyl, which are optionally substituted by trifluoromethyl, halogen or straight-chain or branched alkyl having up to 6 carbon atoms,

Q represents an oxygen or sulfur atom,

and salts thereof.

2. 3-Ureido-pyridofurans and -pyridothiophenes according to the formula of claim 1, in which

E, G, L and M are identical or different and represent a nitrogen atom or a residue of a formula -C-A, wherein at least one of the substituents E, G, L or M must represent a nitrogen atom and wherein

A represents hydrogen, straight-chain or branched acyl or alkoxycarbonyl each having up to 6 carbon atoms, or straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by chlorine, bromine, hydroxyl, carboxyl, straight-chain or branched alkoxycarbonyl or alkoxy each having up to 5 carbon atoms, phenoxy, benzoyl, or by a group of a formula -O-CO-CH₃, or represents fluorine, chlorine, bromine, nitro, trifluoromethyl or a group of a formula -OR⁵, -S(O)_nR⁶, (O-CH₂-CO)_b-NR⁷R⁸, -CO-NR⁹R¹⁰, -SO₂-NR¹¹R¹² or -NH-SO₂R¹³,

in which

R⁶, R⁸, R¹⁰ and R¹² are identical or different and denote hydrogen, cyclopropyl, cyclopentyl, cyclohexyl, chinolyl, pyridyl, imidazolyl, 1,3-thiazolyl or thienyl, which are optionally substituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, cyano, nitro or by a straight-chain or branched alkyl having up to 5 carbon atoms,

denote straight-chain or branched alkyl, alkenyl or acyl each having up to 6 carbon atoms, or

denote phenyl, which is optionally monosubstituted to disubstituted by identical or different substituents from the series comprising nitro, fluorine, chlorine, bromine, iodine, carboxyl or straight-chain or branched alkoxycarbonyl having up to 5 carbon atoms,

R⁷, R⁹ and R¹¹ are identical or different and

denote hydrogen or a straight-chain or branched alkyl having up to 3 carbon atoms,

or

5 R^7 and R^8 together with the nitrogen atom form a pyrrolidinyl or piperidinyl ring,

R^5 has the abovementioned meaning of R^6 , R^8 , R^{10} or R^{12} and is identical or different from the latter,

or

10 R^5 denotes benzyl, acetyl or tetrahydropyranyl or straight chain or branched alkoxycarbonyl having up to 4 carbon atoms,
denotes straight-chain or branched alkyl having up to 6 carbon atoms, which is optionally substituted by carboxyl, hydroxyl, straight-chain or branched acyl, oxyacyl or alkoxy-carbonyl each having up to 4 carbon atoms, phenoxy,
15 benzoyl or by pyridyl, imidazolyl, thenyl or furyl, which are optionally substituted by fluorine, chlorine, bromine, cyano, nitro or by straight-chain or branched alkyl having up to 4 carbon atoms,

20 and/or alkyl is substituted by a group of a formula
 $-(CO)_c-NR^{14}R^{15}$,

in which

R^{14} and R^{15} are identical or different and have the above mentioned meaning of R^7 and R^8 ,

and

25 c denotes a number 0 or 1,

or

R^5 denotes a group of a formula $-SO_2R^{16}$,

in which

R^{16} denotes phenyl, trifluormethyl or straight-chain or branched alkyl having up to 3 carbon atoms,

5 a denotes a number 0, 1 or 2,

 b denotes a number 0 or 1,

R^{13} has the abovementioned meaning of R^{16} and is identical or different from the latter,

or

10 E and G represent the CH-group,

and

L and M represent a residue of a formulae $-CD$ and $-CD'$,

in which

D and D' together form a pyridine ring,

15 R^1 represents hydrogen, straight-chain or branched alkyl having up to 4 carbon atoms, tert.butoxycarbonyl or a group of the formula $-CO-R^{17}$

in which

20 R^{17} denotes hydroxyl, straight chain or branched alkoxycarbonyl having up to 4 carbon atoms, cyclopentyl, cyclohexyl, pyridyl, pyrrolidinyl or straight chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by fluorine, chlorine, bromine, carboxyl or straight chain or branched alkoxycarbonyl having up to 4 carbon atoms, or

denotes phenyl, which is optionally substituted by hydroxyl, carboxyl or straight chain or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms,

T represents an oxygen or sulfur atom,

5 R² and R³ are identical or different and represent hydrogen, cyclobutyl, cyclopentyl, cyclohexyl or straight-chain or branched alkyl, alkoxycarbonyl or alkenyl each having up to 6 carbon atoms, or
represent benzoyl or phenyl, which are optionally monosubstituted to
10 trisubstituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, iodine, carboxyl, cyano, nitro or by a straight-chain or branched alkyl, alkoxy or alkoxycarbonyl each having up to 5 carbon atoms, or
represent a group of a formula -P(O)(OR¹⁸)(OR¹⁹)

in which

15 R¹⁸ and R¹⁹ are identical or different and denote straight chain or branched alkyl having up to 4 carbon atoms

or

R² and R³ together with the nitrogen atom form a pyrrolidinyl, piperidinyl or morpholinyl ring,

20 and

R⁴ represents phenyl or
represents pyridyl, pyrimidyl, pyrrol, imidazolyl, pyrazolyl, thienyl, iso-
thiazolyl, pyrazinyl, thiazolyl or benzo[b]thiophenyl, wherein both rings are
optionally monosubstituted to trisubstituted by identical or different sub-
25 stituents from the series comprising hydroxyl, fluorine, chlorine, bromine, nitro, tetrazolyl, pyridyl, trifluoromethyl, trifluoromethoxy, difluoromethyl, difluoromethoxy, cyano, carboxy, straight-chain or branched alkoxy, alkoxycarbonyl or acyl each having up to 6 carbon atoms, or by straight-chain or branched alkyl having up to 4 carbon atoms, which is optionally

substituted by carboxyl or straight-chain or branched alkoxy carbonyl having up to 4 carbon atoms,

and

Q represents an oxygen or sulfur atom,

5 and salts thereof.

3. 3-Ureido-pyridofurans and -pyridothiophenes of the formula according to claim 1, in which

10 E, G, L and M are identical or different and represent a nitrogen atom or a residue of a formula -C-A, wherein at least one of the substituents is E, G, L or M, must represent a nitrogen atom and wherein

15 A represents hydrogen, acetyl, straight-chain or branched alkoxy or alkoxy carbonyl having up to 4 carbon atoms, straight-chain or branched alkyl having up to 5 carbon atoms, which is optionally substituted by bromine or by a group of a formula O-CO-CH₃, methoxy or hydroxyl
or

20 represents fluorine, chlorine, bromine, carboxyl, cyano, hydroxyl, nitro, trifluoromethyl, or a group of the formula -OSO₂-CH₃, -O-CH₂CH=CH₂, -O-CH₂-CO-pyrrolidine, -O(CH₂)₂-pyrrolidine, -O(CH₂)₂-piperidine, -O-(CH₂)₄-O-C(O)-CH₃ or -O-(CH₂)₂-O-(C(O)-CH₃

or

E and G represents the CH-group,

and

25 L and M represent a residue of a formulae -CD and -CD'

in which

D and D' together form a pyridine ring,

R¹ represents hydrogen or straight-chain or branched alkyl having up to 3 carbon atoms,

5 T represents an oxygen or sulfur atom,

R² and R³ are identical or different and represent hydrogen, straight-chain or branched alkyl having up to 5 carbon atoms, or represent benzoyl or phenyl, or represent a group of a formula -P(O)(OC₂H₅)₂,

10 and

R⁴ represents phenyl or represents pyridyl, pyrimidyl, furyl, thienyl, imidazolyl, pyrrolyl, thiazolyl or pyrazinyl which are optionally up to difold substituted by identical or different pyridyl, nitro, fluorine, chlorine, bromine, methoxy, trifluoro-methyl, cyano, or by straight-chain or branched alkyl having up to 3 carbon atoms, which is optionally substituted by carboxyl or straight-chain or branched alkoxycarbonyl having up to 3 carbon atoms

and

Q represents an oxygen or sulfur atom,

20 and salts thereof.

4. 3-Ureido-pyridofurans and -pyridothiophenes of the formula according to claim 1, in which

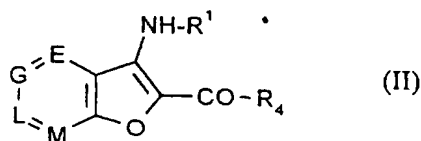
R¹ and R² represent hydrogen,

R^4 represents phenyl, pyridyl or thienyl, which are optionally mono- or disubstituted by chlorine, bromine, fluorine, nitro, methoxy or straight-chain or branched alkyl having up to 3 carbon atoms.

5 5. 3-Ureido-pyridofuranes and -pyridothiophenes according to claim 1 to 4 as medicaments.

6. Process for the preparation of 3-ureido-pyridofuranes and -pyridothiophenes according to claim 1 to 4, characterized in that

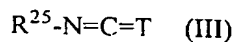
compounds of the general formula (II)



10 in which

E, G, L, M, R^1 and R^4 have the abovementioned meaning

are reacted with compounds of the general formula (III)



in which

15 T has the abovementioned meaning

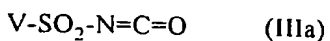
and

R^{25} has the abovementioned meaning of R^2 and R^3

in inert solvents, if appropriate in the presence of a base and/or in the presence of an auxiliary,

20 and in the case of $R^2/R^3 = H$ and $T = O$,

compounds of the general formula (II) are reacted with compounds of the general formula (IIIa)



in which

5 V denotes halogen, preferably chlorine,

and in the case of $\text{R}^2/\text{R}^3 = \text{H}$ and $\text{T} = \text{S}$,

compounds of the general formula (II) are reacted with NH_4SCN ,

and in case of R^1 , R^2 and/or $\text{R}^3 \neq \text{H}$ the amino groups are derivated optionally by customary methods.

10 and in the case of $\text{A} = \text{OSO}_2\text{R}^{16}$ the corresponding hydroxyl compounds are reacted with sulfonylchloride derivatives in presence of K_2CO_3 .

7. A composition comprising a 3-urea-pyridofuran or -pyridothiophene according to claim 1 to 4 and a pharmacologically acceptable diluent.

8. A composition according to claim 7 for the treatment of acute and chronic
15 inflammatory processes.

9. Use of 3-urea-pyridofurans and -pyridothiophenes according to claim 1 to 4 for the preparation of medicaments.

10. Use according to claim 9 for the preparation of medicaments for the treatment of acute and chronic inflammatory processes.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 97/03432

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/048 A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	EP 0 779 291 A (BAYER AG) 18 June 1997 see the whole document ---	1-10
P,X	EP 0 731 099 A (BAYER AG) 11 September 1996 see the whole document ---	1-10
Y	EP 0 623 607 A (BAYER AG) 9 November 1994 see the whole document ---	1-10
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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